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(54) Title: BIODEGRADABLE MACROMERS FOR THE CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE SUBSTANCES

(57) Abstract

A method for delivering a biologically active substance including the steps of: (a) combining said biologically active substance with a macromer; (b) forming a mixture of the combination formed in step (a); (c) polymerizing said mixture to form articles; and (d) administering said articles, or a portion thereof, to a mammal, where step (c) takes place in the absence of a polymerizable monovinyl monomer, is disclosed.

BIODEGRADABLE MACROMERS FOR THE CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE SUBSTANCES

Background of the Invention

The invention relates to methods for administering biologically active substances, and biodegradable compositions for administering these substances.

The rapid advances in the fields of genetic engineering and biotechnology have led to the development of an increasing number of proteins and peptides that are useful as pharmaceutical agents. The development of methods for administering these new pharmaceutical agents is thus gaining increasing importance. In particular, the local or systemic administration of biologically active substances, such as proteins, is a current concern.

The delivery of proteins can be complicated, as proteins will degrade in many of the carriers that have traditionally been used for the administration of small molecules. In many cases, the active forms of proteins are difficult to formulate in biodegradable polymers. Synthetic materials, such as biodegradable hydrogels, can be used to deliver proteins. In many methods, however, the delivery of the protein to the systemic and local circulation is relatively rapid, and is determined primarily by the rate of dissolution of the protein particles. These methods can be of limited utility, as drug release can occur in an initial "burst" rather than at a sustained, controlled rate.

Summary of the Invention

In a first aspect, the invention features a method for delivering a

Claims

1. A method for delivering a biologically active substance, said method comprising the steps of:

(a) combining said biologically active substance with a macromer;

(b) forming a mixture of the combination formed in step (a);

(c) polymerizing said mixture to form articles; and

(d) administering said articles, or a portion thereof, to a mammal, wherein step (c) takes place in the absence of a polymerizable monovinyl monomer.

2. A method for delivering a biologically active substance, said method comprising the steps of:

(a) combining said biologically active substance with a macromer;

(b) forming a mixture of the combination formed in step (a);

(c) polymerizing said mixture to form articles; and

(d) administering said articles, or a portion thereof, to a mammal, wherein step (c) takes place in the absence of a water soluble polymerizable monovinyl monomer.

3. A method for delivering a biologically active substance, said method comprising the steps of:

(a) combining said biologically active substance with a macromer;

(b) forming a mixture of the combination formed in step (a);

(c) polymerizing said mixture to form articles; and

(d) administering said articles, or a portion thereof, to a mammal, wherein step (c) takes place in the absence of a vinyl pyrrolidone monomer.

4. The method of claim 1, wherein the time during which 10% of the releasable active substance is released is greater than 1/10 of t_{50}.

5. The method of claim 1, wherein said article comprises at least 2.5% active substance by weight.

6. The method of claim 1, wherein said article comprises at least 5% active substance by weight.

7. The method of claim 1, wherein said article comprises at least 10% active substance by weight.

8. The method of claim 1, wherein said article comprises at least 25% active substance by weight.

9. The method of claim 1, wherein said article comprises at least 40% active substance by weight.

10. The method of claim 1, wherein said macromer comprises:

(a) a water soluble region forming a central core;

(b) at least two degradable regions attached to said core; and

(c) at least two polymerizable end groups, wherein said polymerizable end groups are attached to said degradable regions.

11. The method of claim 10, wherein said water soluble region comprises a polymer selected from the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone),

poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers, polysaccharides, carbohydrates, proteins, and combinations thereof.

12. The method of claim 10, wherein said degradable region comprises a polymer selected from the group consisting of poly(α-hydroxy acids), poly(lactones), poly(amino acids), poly(anhydrides), poly(orthoesters), poly(orthocarbonates) and poly(phosphoesters).

13. The method of claim 10, wherein said degradable region comprises poly(trimethylene carbonate).

14. The method of claim 10, wherein said degradable region comprises poly(caprolactone).

15. The method of claim 12, wherein said poly(α-hydroxy acid) is selected from the group consisting of poly(glycolic acid), poly(DL-lactic acid) and poly(L-lactic acid).

16. The method of claim 12, wherein said poly(lactone) is selected from the group consisting of poly(ϵ-caprolactone), poly(δ-valerolactone), and poly(γ-butyrolactone).

17. The method of claim 10, wherein said polymerizable end groups contain a carbon-carbon double bond capable of polymerizing the macromers.

18. The method of claim 10, wherein said core comprises

poly(ethylene glycol); said degradable regions comprise a biodegradable poly(α-hydroxy acid); and said end caps comprise an acrylate oligomer or monomer.

19. The method of claim 1, wherein step (d) comprises administering said articles to the lung of said mammal.

20. The method of claim 1, wherein step (d) comprises administering said articles intravenously.

21. The method of claim 1, wherein step (d) comprises administering said articles subcutaneously.

22. The method of claim 1, wherein step (d) comprises administering said articles intramuscularly.

23. The method of claim 1, wherein step (d) comprises administering said articles orally.

24. The method of claim 1, wherein step (d) comprises administering said articles nasally.

25. The method of claim 1, wherein said mammal is a human.

26. The method of claim 1, wherein said biologically active substance is a protein.

27. A composition formed by the method of claim 1.

28. A composition formed by the method of claim 2.

29. A composition formed by the method of claim 3.

30. A method for delivering a biologically active substance, said method comprising the steps of:

(a) combining said biologically active substance with a macromer;

(b) forming a mixture of the combination formed in step (a);

(c) polymerizing said mixture to form articles; and

(d) administering said articles, or a portion thereof, to a mammal, wherein said articles release at least 80% of said biologically active substance at a time 2.5 times greater than t_{50}.

31. A method for delivering a biologically active substance, said method comprising the steps of:

(a) combining said biologically active substance with a macromer;

(b) forming a mixture of the combination formed in step (a);

(c) polymerizing said mixture to form articles; and

(d) administering said articles, or a portion thereof, to a mammal, wherein said articles release a therapeutic dose of said biologically active substance for a period of time at least 2.5 times greater than t_{50}.

32. A composition for delivering a biologically active substance, said composition comprising particles comprising a hydrogel and a biologically active substance, wherein the release kinetics of said particles are independent

of particle size, wherein said particles have a mass mean diameter of about 50 nm to about 1 mm.

33. A method for making articles for controlled release of a biologically active substance, said method comprising the steps of:

(a) combining said biologically active substance with a biodegradable, polymerizable macromer, said macromer comprising at least one water soluble region, at least one degradable region which is hydrolyzable under *in vivo* conditions, and polymerizable end groups having the capacity to form additional covalent bonds resulting in macromer polymerizing, wherein said polymerizable end groups are separated by at least one degradable region, in the presence of an initiator;

(b) polymerizing said macromer in the absence of light to form a hydrogel and to incorporate said biologically active substance into said hydrogel; and

(c) forming said hydrogel into articles capable of controlled release of said biologically active substance.

34. The method of claim 33, wherein said initiator is a radical initiator.

35. The method of claim 33, wherein said initiator is an ionic initiator.

36. A method for making a polymerized hydrogel, said method comprising the steps of:

(a) combining a hydrophobic, water insoluble macromer, an initiator,